REMARKS

Reconsideration and withdrawal of the rejections of this application and consideration and entry of this paper are respectfully requested in view of the herein remarks, which place the application in condition for allowance.

I. STATUS OF CLAIMS AND FORMAL MATTERS

Claims 1, 3-5 and 8-11 are pending. Claims 2, 6 and 7 are cancelled and claims 1, 3-5 and 9-10 are amended without admission and without surrender of any subject matter as to equivalents.

No new matter is added.

It is submitted that the claims, as originally presented, and as herewith presented, are patentably distinct over the prior art cited by the Examiner, and that these claims are in full compliance with the requirements of 35 U.S.C. §112. Changes to claims and/or new claims as presented herein are not made for the purpose of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112. Rather, these changes are made simply for clarification and to round out the scope of protection to which Applicants are entitled.

Support for the amended claims 1, 3-5 and 9-10 can be found throughout the specification and from the cancelled claim.

Consideration and entry of this paper is solicited.

II. CLAIM OBJECTIONS ARE OVERCOME

Claims 1, and 8-11 are objected to for allegedly encompassing a non-elected invention. The objection is traversed. Claims 1 and 9 are amended to recite a "protein agent" as reflected in the election of Group I drawn to a composition comprising specific protein agents, a kit thereof and a method of preventing or treating specific conditions using the composition.

The Examiner is thanked for pointing out the inadvertently omitted term in claim 10. Claim 10 is amended to include the term "inducer" thereby obviating the objection.

III. THE REJECTIONS UNDER 35 U.S.C. §112, 2ND PARAGRAPH, ARE OVERCOME

Claims 1, 3-5 and 8-11 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite.

Claim 1 is amended to recite "therapy for preventing or treating restenosis and/or atherosclerosis" thereby obviating the rejection.

Claims 1 and 9 are amended to delete the terms in parenthesis thereby rendering the rejection moot.

Claim 9 is further amended to clarify the interrelationships between the elements of the kit thereby obviating the rejection.

With regard to the assertion of the Office Action that the term "vessel maturation inducer" in claims 1, 4, 5, 9 and 10 is allegedly not a recognized term in the art and therefore it is allegedly unclear what is meant by "vessel maturation inducer" and the agents that are encompassed by this term. It is respectfully submitted that the Applicants are entitled to be their own lexicographer, and the fact that the term "vessel maturation inducer" is not regarded by the Examiner as a recognized term in the art is irrelevant because it is defined clearly in the instant specification at page 3, lines 6-8 where it clearly states that:

> The present invention also relates to methods and compositions for administering **an agent which induces vessel maturation**, and which **thereby may inhibit the development of vessel sprouting and thereby the development of new vessels e.g., ang-1.**

Further, the agents encompassed by this term "vessel maturation inducer" are clearly described in the specification at page 19, lines 7-14, where it clearly states that:

> With respect to **agents which induce vessel maturation, e.g., ang-1**, it is noted that VEGF and angiopoietins, along with their receptors are important regulators (Koblizek et al. Curr Biol 8(9):529-32 (April 1998)). **Ang-1 and ang-2 modulate VEGF** (Asahara et al. Cir Res 83(3):233-40 (August 1998)). Ang-2 has been recognized as an antagonist for ang-1 and Tie-2 (Maisonpierre et al. Science 277(5322):55-60 (July 1997)). Also, it has been observed that excess soluble Tie-2 abolishes the chemotactic response of endothelial cells towards ang-1; and that ang-2 dose-dependently blocks directed migration towards ang-1, consistent with ang-2 being an inhibitor of ing-1 (Witzenbichler et al. J Biol Chem 273(29):18514-21 (July 1998)).

Therefore the rejection is improper and should be withdrawn.

Claims 4 and 5 are amended to recite "angiopoeitin-1"thereby obviating the rejection.

Claim 3 is amended to recite "wherein the VEGF inhibitor is a soluble VEGF receptor" thereby rendering this rejection moot.

Consequently, reconsideration and withdrawal of the rejections is believed to be in order and such action is respectfully requested.

IV. THE REJECTIONS UNDER 35 U.S.C. §112, 1ST PARAGRAPH, ARE OVERCOME

Claims 1, 3,4 and 8-11 were rejected under 35 U.S.C.§112, first paragraph, as allegedly being non-enabling. The rejection is traversed.

The instant invention is clearly enabled because a skilled artisan would readily understand how to make and use the invention. According to the Court of Appeals for the Federal Circuit in the case of *In re Wands*, 8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988),

> Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. 'The key word is undue, not experimentation.' The determination of what constitutes undue experimentation in a given case requires the application of standard of reasonableness, having due regard for the nature of the invention and the state of the art. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should
> proceed ... [Citations omitted].

Id. at 1404.

Against this background, determining whether undue experimentation is required to practice a claimed invention turns on weighing many factors summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988) For example, (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples of the invention; (4) the nature of the

invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims.

Applying *Wands* to the instant facts, it is clear that enablement exists, to wit, *inter alia*, that the quantity of experimentation necessary is low; the amount of direction or guidance presented is high; working examples are clearly present; the relative skill of those in the art is high; and the predictability of the art is also high.

It is respectfully asserted that the instant invention is clearly enabled because a skilled artisan would readily understand how to identify protein agents with the desired activity and prepare the claimed compositions for the prevention or treatment of atherosclerosis or restenosis. Further, the Examiner is directed to the instant specification which states that : 1) An agent for inhibiting VEGF can be obtained by purification from natural sources or from purification from recombinant sources; and, techniques for such purifications or for protein purification are generally known and require no undue experimentation by the skilled artisan (see page 23, lines 13-16). Also, it is matter of routine optimization for the skilled artisan to utilize either the apoE knockout mouse or the porcine coronary artery injury model as described in Examples 1-3 for the identification of particular VEGF inhibitors and a vessel maturation inducers that could potentially prevent or treat atherosclerosis or restenosis, 2) The methods for making and/or administering a vector or recombinant for expression of such agents either *in vivo* or *in vitro* (see page 23, line 18 to 25, line 12), 3). The expression product generated by vectors or recombinants in this invention can also be isolated from infected or transfected cells and used to prepare compositions for administration to patients (see page 25, lines 13-15), 4) Compositions for use in the present invention can be prepared in accordance with standard techniques well known to those skilled in the pharmaceutical or medical arts (see page 15, line 16 to page 26, line 8), 5) Dosages of each active agent for administration are described at page 26, line 18 to page 27, line 9 of the specification, and 6) Plasmid compositions at page 27, lines 10-18). Further, Example 1 details the administration of an agent inhibiting VEGF (e.g., the soluble VEGF receptor) and an agent inducing vessel maturation (e.g., ang-1) to an apoE knockout mice (see Fig 2). More specifically, the apoE knockout mice were treated by intraperitoneal administration of a protein inhibitor of the VEGF pathway (e.g., the soluble VEGF receptor), and with

ang-1. These agents were administered as frequently as possible, with the maximal amount determined by the LD50 and by the availability of protein. Endpoint measurements were used to determine whether the proposed strategy had biologic effects, vessels were obtained at various timepoints from the apoE knockout mice either treated or not treated with: 1) ang-1 protein (by immunohistochemistry and/or by Western analysis), 2) tyrosine kinase phosphorylation of TIE 2 (to assess the state of activation of the receptor), 3) VEGF protein (by immunohistochemistry and/or by Western analysis), 4) tyrosine kinase phosphorylation of one or more of the VEGF receptors (to assess the state of activation of the receptor), 5) atherosclerotic mass (measured by usual computerized image analysis techniques), 6) the magnitude of vasovasorum development measured by microscopic CT, and 7) the magnitude of vasovasorum development measured by immunohistochemistry staining for endothelial cells. This methodology can easily be extrapolated to any agent inhibiting VEGF or any agent inducing vessel maturation without undue experimentation.

Example 3 describes the formulations or use of the compositions of the instant invention and can easily and without undue experimentation be extrapolated to any agent inhibiting or any agent inducing vessel maturation.

In addition, predictability in the art did exist at the time of filing and, coupled with the knowledge of a skilled artisan and the guidance of the present application, there is sufficient evidence that Applicants' disclosure does satisfy the enablement requirement.

With regard to the Office Action's assertion that claim 8 and 9 are allegedly not enabled for "preventing" atherosclerosis or restenosis. Applicants respectfully submit that as described in the instant specification as follows:

> For prevention of restenosis, the compositions, alone or with other treatment, may be administered at the **first indication of the patient being prone to restenosis, or as soon thereafter as desired by the skilled medical practitioner**, e.g., within six months prior to, immediately prior to, or at angioplasty, such as within six weeks prior to, immediately prior to, or at angioplasty, in any desired regimen such as a single administration or multiple administrations in a regimen as desired, e.g., monthly, bi-monthly, biannually, or any combination thereof, without any undue experimentation required. Further, for prevention of restenosis, the compositions, alone or with other treatment, may be administered

after or during angioplasty in a regimen of single or multiple administrations as desired by the skilled medical practitioner, such as immediately after, within six weeks after, within six months after, and/or within a year after, e.g., monthly, bi-monthly, biannually, annually, or in some other regimen, by the skilled medical practitioner for such time as is necessary to prevent clogging of blood vessels or symptoms or signs of restenosis, without any undue experimentation required.

One of ordinary skill in the art would be able to determine those individuals susceptible to restenosis or atherosclerosis via familial determination or via routine procedures such as an electrocardiogram (ECG). It is not unreasonable to assume that administering the compositions of the instant invention comprising a protein agent inhibiting VEGF (e.g., the soluble VEGF receptor), and/or a protein agent inducing vessel maturation (e.g., ang-1 or an agent which induces ang-1), and/or a protein agent that inhibits ang-2 (ang-2 inhibits ang-1, would inhibit atherosclerosis (e.g., as shown by the apoE knockout mouse model) thereby reducing restenosis (e.g., as shown by the porcine coronary artery injury model) and therefore restenosis or atherosclerosis in susceptible individuals can be prevented (see page 19, lines 1-6).

Consequently, it is respectfully asserted that, *inter alia*, the specification, the examples, the level of a skilled artisan and predictability in the art all point to enablement, not to undue experimentation.

Consequently, reconsideration and withdrawal of the Section 112 rejection is believed to be in order and such action is respectfully requested.

V. THE SECTION 103 REJECTIONS ARE OVERCOME

Claims 1, 3-5 and 8-11 are rejected under 35 U.S.C. §103(a) as allegedly obvious over Inoue et al. (Circulation, 1998, 98(20):2108-16) and Maisonpierre et al. (Science, 1997, 277:55-60) in view of Kendall et al. (U.S. Pat. No. 5,712,380) and Asahata et al. (Circ. Res., 1998, 83:233-240). The rejections will be addressed cumulatively and are traversed.

The Office Action alleges that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to make a composition comprising a VEGF inhibitor, such as a soluble VEGF receptor, and ang-1 and to use it to treat atherosclerosis/restenosis because of the teachings of Inoue and Maisonpierre, namely

that occlusive atherosclerosis lesions have extensive neovascularization, and intense VEGF expression, allegedly suggesting that VEGF promotes the process of atherosclerosis (Inoue's teaching) which may provide an indication to apply a VEGF inhibitor for the condition; and that ang-2, an antagonist of ang-1, promotes continued remodeling or the initiation of vascular sprouting in the context of simultaneous VEGF exposure, and therapeutic manipulation of vessel growth may require simultaneous regulation of both the VEGF and angiopoietin systems (Masionpierres' teaching) thereby allegedly suggesting a combination therapy of a VEGF inhibitor and ang-1.

Reconsideration and withdrawal of these rejections are respectfully requested, especially since the cited documents do not teach or suggest the present invention. The present claims pertain to *inter alia,* a composition for therapy for preventing or treating restenosis and/or atherosclerosis comprising a protein agent for inhibiting VEGF and a protein agent for inducing vessel maturation (claim 1), the composition of claim 12 wherein at least one of the VEGF inhibitor and the vessel maturation inducer comprises an expression system which expresses at least one of the VEGF inhibitor and the vessel maturation inducer, methods (claim 8) and kits (claims 9-11 and 13) thereof; the art fails to teach or suggest the instant invention.

None of the cited references (alone or in any combination) disclose, suggest, or motivate a skilled artisan to practice the presently claimed invention. The Examiner is respectfully reminded of the case law; namely, that there must be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference teachings. *In re Laskowski*, 12 U.S.P.Q. 2d 1397, 1399 (Fed. Cir. 1989); *In re Obukowitz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993). Further, "obvious to try" is not the standard under 35 U.S.C. §103. *In re Fine,* 5 U.S.P.Q. 2d 1596, 1599 (Fed. Cir. 1988). And, as stated by the Court in *In re Fritch*, 23 U.S.P.Q. 2d 1780, 1783-1784 (Fed. Cir. 1992): "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification." Also, the Examiner is respectfully reminded that for the Section 103 rejection to be proper, **both the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicants' disclosure**. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988).

Inoue et al. teaches vascular endothelial growth factor (VEGF) expression in human coronary atherosclerotic lesions and that VEGF may have some role in the progression of human coronary atherosclerosis. There is no teaching or suggestion of any type of VEGF inhibitor let alone the combination of a VEGF inhibitor and a vessel maturation inducer for the treatment of restenosis or atherosclerosis.

Maisonpierre et al. describes angiopoietin-2, a natural antagonist for Tie2 that disrupts in vivo angiogenesis. Again, there is no teaching or suggestion of the application of both a VEGF inhibitor and a vessel maturation inducer for the treatment of restenosis or atherosclerosis. In addition, for a Section 103 rejection to be proper, both the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicants' disclosure. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). There is no such disclosure in Maisonpierre et al., therefore the 103 is improper and should be withdrawn.

Kendall teaches a VEGF receptor protein and an inhibitor thereof. There is no teaching or suggestion of the application both a VEGF inhibitor and a vessel maturation inducer for the treatment of restenosis or atherosclerosis. In addition, no reasonable expectation of success can be gleaned from reading the disclosure of Kendall et al., therefore the 103 rejection cannot stand and should be withdrawn.

Asahara et al. discloses that Tie2 receptor ligands, angiopoietin-1 and angiopoietin-2, modulate VEGF-induced postnatal neovascularization. There is no teaching or suggestion of the application both a VEGF inhibitor and a vessel maturation inducer for the treatment of restenosis or atherosclerosis. In addition, for a Section 103 rejection to be proper, both the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicants' disclosure. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). There is no such disclosure in Asahara et al., therefore the 103 is improper and should be withdrawn.

In addition, the finding of Inoue et al. that VEGF is expressed in atherosclerotic lesions and that Ang-1 and ang-2 have been shown to modulate VEGF (Asahara et al. Cir Res 83(3):233-40 (August 1998)) and that furthermore Ang-2 has been recognized as an antagonist for ang-1 and Tie-2 (Maisonpierre et al. Science 277(5322):55-60 (July 1997)) has no implications for the present invention. All of these findings in the cited references

are preliminary with no suggestion or teaching of how these findings can be used to prevent or treat atherosclerosis or restenosis. In addition, the VEGF system involved in the regulation of angiogenesis is a complex process with many multifaceted steps. Finding modulators of VEGF as VEGF is only one of many molecular systems thought to be implicated in the formation or pathobiology of blood vessels and does not guarantee a therapy for atherosclerosis or restenosis. Also contrary to the view of the Office Action, the disclosure of Kendall or Asahara et al. which simply disclose that ang-2 and VEGF are required for neovascularization, does not suggest that inhibiting both would effectively prevent restenosis. Therefore none of Inoue et al., Maisonpierre et al. Kendall et al., or Ashara et al. suggest or motivate a skilled artisan to practice Applicants' invention.

Consequently, reconsideration and withdrawal of the Section 103 rejections are believed to be in order and such action is respectfully requested.

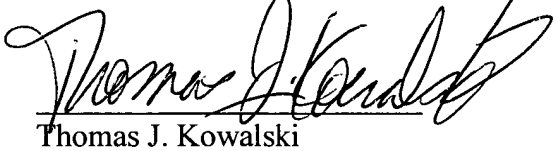
REQUEST FOR INTERVIEW

If any issue remains as an impediment to allowance, an interview with the is respectfully requested, prior to issuance of any paper other than a Notice of Allowance; and, the Examiner is respectfully requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

CONCLUSION

In view of the remarks and amendments herewith and those of record, the application is in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance, or an interview at a very early date with a view to placing the application in condition for allowance, are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date.

Respectfully submitted,
FROMMER LAWRENCE & HAUG LLP

By: 

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Marked Up Version To Show Changes Made

1. (Amended) A composition for therapy for preventing or treating restenosis and/or atherosclerosis comprising [an] a protein agent for inhibiting VEGF [(VEGF inhibitor)] and [an] a protein agent for inducing vessel maturation [(vessel maturation inducer)].

3. (Amended) The composition of claim 1 wherein the protein agent for inhibiting VEGF [inhibitor comprises the] is a soluble VEGF receptor.

4. (Amended) The composition of claim 1 wherein the protein agent for inducing vessel maturation [inducer] comprises angiopoeitin-1 [ang-1].

5. (Amended) The composition of claim 3 wherein the vessel maturation inducer comprises angiopoeitin-1 [ang-1].

9. (Amended) A kit for formulating a composition for preventing or treating atherosclerosis or restenosis as claimed in claim [8] 1 by admixture comprising [an] the protein agent for inhibiting VEGF [(VEGF inhibitor)] and [an] the protein agent for inducing vessel maturation [(vessel maturation inducer)].

10. (Amended) The kit of claim 9 wherein the protein agent for inhibiting VEGF inhibitor and the protein agent for inducing vessel maturation are in separate containers.